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CITATIONS





477-696—72——1

Statutes:

# In the Supreme Court of the United States

OCTOBER TERM, 1972

No.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, PETITIONERS

*v.*

BENTEX PHARMACEUTICALS, INC., ET AL.

## PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

The Solicitor General, on behalf of the Secretary of Health, Education, and Welfare and the Commissioner of Food and Drugs, petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Fourth Circuit in this case.

### OPINIONS BELOW

The opinion of the court of appeals (App. A, *infra*, pp. 1a–17a) is not yet officially reported. The opinion of the district court (App. C, *infra*, pp. 19a–29a) is not reported.

### JURISDICTION

The judgment of the court of appeals was entered on May 23, 1972 (App. B, *infra*, p. 18a). Mr. Justice Rehnquist extended the time within which to file a

petition for a writ of certiorari to October 5, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

## QUESTION PRESENTED

Whether the Food and Drug Administration has jurisdiction to determine initially whether a product is a "new drug" which must be administratively approved as safe and effective before it can be sold in commerce.

## STATUTES INVOLVED

Relevant provisions of the Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040, as amended by the Harris-Kefauver Act, 76 Stat. 780, 21 U.S.C. 301 *et seq.*, are set forth in Appendix D, *infra*, pp. 30a–32a.

The Administrative Procedure Act, 5 U.S.C. 551–559, 701–706, provides in pertinent part:

> § 554(e). The agency, with like effect as in the case of other orders, and in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty.
>
> § 703. The form of proceeding for judicial review is the special statutory review proceeding relevant to the subject matter in a court specified by statute or, in the absence or inadequacy thereof, any applicable form of legal action, including actions for declaratory judgments or writs of prohibitory or mandatory injunction or habeas corpus, in a court of competent jurisdiction. * * *
>
> § 704. Agency action made reviewable by statute and final agency action for which there is no other adequate remedy in a court are subject to judicial review. * * *

## STATEMENT

This case, like *Richardson* v. *Hynson, Westcott and Dunning, Inc.*,[1] arises out of efforts by the Food and Drug Administration (FDA) to implement its congressionally imposed responsibility to insure that drugs on the market are effective for their intended uses.

In the Federal Food, Drug and Cosmetic Act of 1938, 52 Stat. 1040, Congress established a system of premarketing clearance for drugs. The Act prohibited the introduction of any "new drug" into interstate commerce unless an application approved by FDA was effective with respect to that drug (Section 505(a), 52 Stat. 1052). A "new drug" was defined as any drug not generally recognized by qualified experts as safe for its intended uses (Section 201(p)(1), 52 Stat. 1041–1042). The government could sue to enjoin violations of this prohibition, prosecute criminally, or proceed against the drugs in seizure and condemnation proceedings (Sections 301(d), 302(a), 303, 304, 52 Stat. 1042–1045). The Act established procedures for filing new drug applications (Section 505(b), 52 Stat. 1052) and provided standards under which, after notice and hearing, the agency could refuse to permit a new drug application (NDA) to become effective (Section 505(d), 52 Stat. 1052) or could suspend the effectiveness of an NDA (Section 505(e), 52 Stat. 1053). Such refusal and suspension orders could be reviewed in the district courts on the record made before the agency (Section 505(h), 52 Stat. 1053).

[1] Petition for a writ of certiorari filed Sept. 7, 1972, No. 72–354; cross-petition filed Sept. 11, 1972, No. 72–414.

In 1962, Congress adopted the Harris-Kefauver Amendments to the Act, which imposed new and broadened responsibilities on FDA and provided that, in order to be lawfully marketed, drugs must be *effective* for their intended uses as well as safe. The definition of "new drug" was revised to mean a drug not generally recognized by qualified experts as safe *and effective* for its intended uses (Section 201(p)(1), 21 U.S.C. 321(p)(1)). Congress expressly directed the agency to refuse approval for an NDA, and to withdraw prior approvals, if "substantial evidence" that the drug is effective for its intended uses is lacking (Sections 505(d) and (e), 21 U.S.C. 355(d) and (e)).[2] Thus, the basic clearance scheme requiring an administratively approved NDA before a "new drug" may be lawfully marketed was continued, as were the provisions for judicial enforcement of this requirement by injunction, seizure and criminal proceedings.[3]

To provide manufacturers an opportunity to develop substantial evidence of effectiveness, the amendments contained a grace period of two years during which previously approved NDAs could not be withdrawn by FDA for lack of effectiveness.[4] The amend-

[2] "Substantial evidence" was defined to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug" will be effective for its intended uses (Section 505(d), 21 U.S.C. 355(d)).

[3] Judicial review of refusals and withdrawals of approval for NDAs was transferred from the district courts to the courts of appeals (Section 505(h), 21 U.S.C. 355(h)).

[4] P.L. 87-781, Section 107(c)(3)(B), 76 Stat. 788-789, note following 21 U.S.C. 321 (1970 ed.).

ments also contained a "grandfather" clause exempting from the effectiveness requirement any drug which on the day preceding enactment (A) was commercially used or sold in the United States, (B) was not a "new drug" as defined in the 1938 Act (*i.e.*, was generally recognized as safe), and (C) "was not covered by an effective [new drug] application" under the 1938 Act.[5]

Of the 7,100 drugs for which approvals had been granted between 1938 and 1962, more than 4,000, involving approximately 16,700 claimed uses, were still on the market. In order to implement the congressional directive that ineffective drugs be removed from the market, FDA initiated a comprehensive efficacy review program—the "Drug Efficacy Study Implementation" (DESI). In 1966, FDA retained the National Academy of Sciences-National Research Council (NAS–NRC) to establish expert panels to review the efficacy claims of previously approved drugs. All holders of NDAs were invited to furnish the NAS–NRC panels the best data available to establish the effectiveness of their drugs (31 Fed. Reg. 9426). The panels then evaluated the material submitted to them and reported to the FDA, classifying the drugs as "effective," "probably effective," "possibly effective" and "ineffective." Drugs in any category other than "effective" are subject to withdrawal of approval.

In addition to the drugs for which NDAs had been issued, there were thousands of similar or identical formulations of other manufacturers that had come on the market without obtaining NDAs, in reliance

[5] P.L. 87–781, Section 107(c)(4), 76 Stat. 789, note following 21 U.S.C. 321 (1970 ed.).

upon the approval granted by FDA to the "pioneer" that they resembled. This case arises in the context of the FDA's efforts to remove these copies, called "me-too" drugs, from the market once the NDA for the ineffective "pioneer" has been withdrawn.

*Proceedings before the FDA.*—Under the pre–1962 standards, the agency had approved NDAs covering pentylenetetrazol combination drugs.[6] The NDAs were held by firms not involved in the present case. Three separate NAS–NRC panels reviewed the available evidence concerning the combinations (C.A. App., pp. E–R),[7] and each panel concluded that the drug was "ineffective" for each of its indicated uses (*id.* at pp. G, H, N, O, P, R).[8]

After evaluating the NAS–NRC reports on drug combinations containing pentylenetetrazol, the FDA concluded that there was a lack of substantial evidence that these drugs are effective for their intended uses. Accordingly, on August 26, 1969, it published a notice (34 Fed. Reg. 13673–13674) announcing its in-

[6] These are prescription drugs offered for senile psychosis and psychoneurosis, with anxiety and nervous tension, senile fatigue, confusion, debilitation, depression, dizzy spells, mild behavioral disorders, irritability and functional memory defects.

[7] "C.A. App." refers to the appendix to the appellees' brief in the court of appeals.

[8] The specific drugs evaluated were NICOZOL with RESERPINE (a combination of pentylenetetrazol, nicotinic acid and reserpine) which was evaluated by the panel on psychiatric drugs (C.A. App., pp. E–I) and GERONIAZOL injection (a combination of pentylenetetrazol and nicotinic acid administered by injection), which was evaluated by the panel on psychiatric drugs (*id.* at pp. N–O), the panel on drugs used in anesthesiology (*id.* at pp. P–Q), and the panel on drugs used in respiratory disturbances (*id.* at p. R).

tention to initiate proceedings to withdraw approval of the NDAs for these drugs. The notice invited the holders of NDAs "and any interested person who might be adversely affected by [the drugs'] removal from the market" to submit, within 30 days, any "adequate and well-controlled studies bearing on the efficacy of" the drugs in question. It also stated that promulgation of an order withdrawing approval of the NDAs would cause any drug containing the same substances to be a "new drug" for which an approved NDA is not in effect, and hence subject to "regulatory action."

Only one firm submitted further material in response. On May 20, 1970, the FDA announced that substantial evidence of effectiveness was lacking and that the prior approvals were to be withdrawn. The three firms which held approved NDAs and "any other interested person who may be adversely affected by such action" were offered an opportunity for a hearing. The agency also again declared that withdrawal of approval for the NDAs would cause any drug containing the same substances to be a "new drug" for which an approved NDA is not in effect. 35 Fed. Reg. 7749. Only one NDA holder requested a hearing, but it filed no material to support its request. The Commissioner therefore withdrew approval for the three NDAs then in effect. 35 Fed. Reg. 14412. No appeal was taken to review this action.

After its decision on the pentylenetetrazol NDAs, the agency took steps to remove from the market all "me-too" drugs containing that product. For example, on November 4, 1970, FDA wrote Bentex Pharma-

ceuticals advising it of FDA's action withdrawing approval for NDAs on drugs similar to Bentex products containing pentylenetetrazol and stating that, in view of this, those Bentex products were no longer marketable (App. C, *infra*, p. 24a, n. 3).

*Decision of the District Court.*—On December 1, 1970, Bentex and 23 other firms that market drugs containing pentylenetetrazol filed this suit for declaratory and injunctive relief. They contended that their drugs containing pentylenetetrazol either are not "new drugs" within the meaning of the amended Act or are exempt from the requirements of the amended Act by virtue of the grandfather clause. They accordingly sought a ruling declaring invalid and unenforceable the Commissioner's position that their drugs are "new drugs" for which no NDA is in effect and which therefore cannot legally be marketed.

The district court held that it had concurrent jurisdiction with the agency to determine whether plaintiffs' drugs are subject to the premarketing clearance procedure of the amended Act (App. C, *infra*, pp. 19a–29a). In so doing, it rejected both the government's contention that FDA has primary and exclusive jurisdiction to determine that issue (*id.* at 26a) and the manufacturers' contention that the question whether their drugs are "new drugs" requiring approved NDAs can be decided only by the district court (*id.* at 25a). The court ruled that the statutory "grant of authority to approve or withhold approval of new drug application [*sic*], or to proceed with regulatory action in the courts [by seizure, criminal prosecution or injunctive proceedings], necessarily implies

authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment" (*ibid.*).

Having found concurrent jurisdiction, the district court concluded that the FDA, as "the more able arbiter of the question," should resolve the "new drug" issue at an administrative hearing in which plaintiffs and any other interested persons could participate (*id.* at 27a).[9] The court entered an injunction to preserve the *status quo,* barring enforcement proceedings against the drugs in question pending resolution of the "new drug" issue by FDA. If the agency declined to hold a hearing, the court said it would then determine the issue (*id.* at 29a).

*Decision of the Court of Appeals.*—On appeal by the plaintiff drug manufacturers,[10] the court of appeals reversed and remanded the case to the district court for it to determine whether plaintiffs' drugs are "new drugs" within the meaning of the Act (App. A, *infra,* pp. 1a–17a). The court of appeals held that the Act confers no jurisdiction on FDA, either primary or concurrent, to adjudicate administratively the question whether a drug is a "new drug" within the meaning of the Act, and that there is thus no basis for referring that question to the agency (*id.* at 12a). The court of appeals reached this conclu-

[9] The district court stated that an appeal from the FDA's determination would lie to the court of appeals (*id.* at 27a). We believe that the FDA's determination in response to the district court's referral order would be reviewable in the district court. See text accompanying note 16, *infra.*

[10] The government did not appeal.

sion because the plaintiffs were not holders of NDAs for these drugs and, under its view of the statutory scheme, "[t]he only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a 'new drug' application" (*id.* at 14a). In the court's view, it is only in the prosecutorial context that FDA is authorized to challenge the status of a drug, and in that context the question whether a product is a "new drug" is exclusively for the courts to decide (*id.* at 12a–13a).

The court of appeals pointed out that the Act does not expressly provide for judicial review of an administrative adjudication of the status of a drug, except in the context of refusal or withdrawal of an NDA. It reasoned that the Act therefore does not confer administrative power to make such an adjudication where no NDA is outstanding and none is sought by the manufacturer (*id.* at 14a–15a).

The court of appeals also rejected the district court's reasoning that the agency has inherent authority to resolve the threshold question of its jurisdiction. No question of whether an article is a "new drug" is presented by the filing of an application, in the court of appeals' view, because the act of applying for approval represents a concession by the manufacturer that the article is a "new drug" (*id.* at 15a). The court held that if the manufacturer chooses not to make that concession, but rather to proceed with marketing at its peril, the courts provide the only forum in which the legality of its actions may be adjudicated.

Since no record had been made in the district court on the issue whether the plaintiffs' drugs are "new

drugs," the case was remanded for determination of that question.

### REASONS FOR GRANTING THE WRIT

The court of appeals' holding that FDA lacks power to determine whether particular drugs require an approved NDA to be lawfully marketed raises an important issue concerning the relationship of the courts and the agency in the administration of the Federal Food, Drug, and Cosmetic Act. It upsets the statutory scheme for administrative pre-market clearance by making the federal courts the exclusive forum for determining, *de novo,* the question on which the agency's jurisdiction turns—whether a product is a "new drug." By inviting transfer to the courts of an enormous volume of litigation concerning this threshold question, the holding below threatens to impair seriously the agency's efforts to remove ineffective drugs from the market. Moreover, the decision conflicts with a recent decision by the Third Circuit (*Ciba Corporation* v. *Richardson,* No. 71–1512, decided June 5, 1972, petition for a writ of certiorari filed October 2, 1972, No. 72–528.

Under Section 505(a) of the Act, a "new drug" may not be sold in interstate commerce unless an NDA for it has been approved by the Food and Drug Administration. A product that is not a "new drug," on the other hand, may be sold freely if not adulterated or misbranded. The agency's jurisdiction, therefore, depends initially on whether a product is a "new drug" within the meaning of the statute. The court below held, however, that the agency is without power to

make this threshold determination and that only the courts may do so. This decision goes to the heart of the scheme for premarketing clearance contemplated by the Act. For, if the agency cannot definitively determine whether a product is a new drug, drug manufacturers cannot look to it to learn with assurance whether their product requires agency approval in order to be marketed. They must either sell the drug in commerce at their own (and the public's) peril, or seek a judicial resolution of the agency's jurisdiction in a declaratory judgment action. Indeed, even if the manufacturer "concedes" that his product is a new drug by filing an application for agency approval, the FDA, under the court of appeals' view, could not determine the jurisdictional question. If the agency denies the application or thereafter withdraws approval, the court of appeals on review would either have to determine the "new drug" question *de novo* or render a decision that, for all practical purposes, is subject to relitigation in a declaratory judgment action.

The decision below would thus effectively transfer to the courts in all instances the determination of the complex medical and pharmacological questions upon which the definition of "new drug" turns. Nothing in the Act requires this unhappy result. On the contrary, Congress assigned to the agency a responsibility affecting the lives and health of millions—to determine in advance of marketing whether drugs are safe and effective. This responsibility carries with it the grant of express and implicit powers necessary for the

achievement of the Act's ultimate purposes.[11] Prominent among these is the power to decide the threshold questions on which the agency's jurisdiction turns.[12]

The Third Circuit's recent decision in *Ciba Corporation* v. *Richardson, supra,* reflects these principles. In that case, the agency withdrew an NDA held by Ciba for Ritonic Capsules. Ciba attacked the withdrawal in two separate judicial proceedings. It petitioned for review of the withdrawal order in the Second Circuit pursuant to Section 505(h) (21 U.S.C. 355(h)), and it filed a declaratory judgment action in a federal district court in New Jersey, claiming that its product was not a "new drug" and therefore was exempt from the Act's requirements. The district court dismissed Ciba's complaint, while the Court of Appeals for the Second Circuit affirmed the agency's withdrawal order. *Ciba-Geigy Corp.* v *Richardson,* 446 F.2d 466. On appeal from the dismissal of its district court action, Ciba contended to the Court of Appeals for the Third Circuit that neither the FDA nor the court of appeals on review of the agency's action had jurisdiction to determine whether Ritonic Capsules are a "new drug" subject to the Act, and that it was entitled to litigate this issue in full in the district court. The court held, however, that the agency necessarily is empowered to decide the threshold question as an incident of its power to approve or withdraw approval of NDAs and that its decision on that issue is review-

[11] See *Permian Basin Area Rate Cases,* 390 U.S. 747, 780; *United States* v. *Southwestern Cable Co.,* 392 U.S. 157, 177–178; *United States* v. *Midwest Video Corp.,* 406 U.S. 649.

[12] Cf. *Oklahoma Press Publishing Co.* v. *Walling,* 327 U.S. 186, 210–211.

able in the courts of appeals on direct appeal from the agency's order:

> Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision.
>
> In disapproving Ritonic Capsules the Commissioner and the Court of Appeals for the Second Circuit necessarily decided that the 1962 amendments of the Act were applicable to that product. * * *

2. The facts of the instant case illustrate the potentially debilitating impact of the decision below on FDA's efforts to discharge its congressionally assigned responsibility to remove ineffective drugs from the market. Following an NAS–NRC finding of ineffectiveness, the agency here made an administrative determination that there is no substantial evidence that drugs containing pentylenetetrazol are effective and withdrew NDAs that had been approved prior to 1962, when safety was the sole criterion. This determination was not appealed and thus became final. However, the action directly affected only the three NDAs that were outstanding for products featuring this drug. Many other manufacturers had products on the market that appeared, in FDA's view, to be mere copies of the drugs found ineffective. Since these "me-too" drugs had never been through the NDA process, although they had apparently come on the market in reliance upon the pioneers' NDAs,

there was no physical piece of paper for FDA to withdraw. Clearly, in FDA's view, if these were in fact the same drugs and were as ineffective as the pioneers, Congress wanted them removed from the market too. The question posed by this case is whether meaningful administrative action toward this end can be taken, or whether all the complex questions involved in the "me-too" area must be resolved exclusively by the courts.

After withdrawal of the pioneers' NDAs, the types of questions raised regarding the status of "me-toos" as new drugs (requiring an approved NDA to remain on the market) can be highly technical and are not well suited for initial determination by the judiciary. For example, a manufacturer may assert that its drug is now generally recognized as safe and effective and is therefore not a "new drug" within the meaning of Section 201(p)(1) of the Act. Although this would be a difficult proposition to establish where the "me-too" drug is identical to the pioneer drug, in light of FDA's finding that substantial evidence of the pioneer drug's effectiveness is lacking, the "me-too" manufacturers may claim, as they did here, that their drugs are significantly different from the pioneers, and that the general recognition of their safety and effectiveness must be separately assessed. The "me-too" manufacturer may also claim exemption from the effectiveness requirement of the Act by virtue of the "grandfather" protection of Section 107(c)(4). Resolution of the grandfather claim would, in the normal case, involve ruling on whether the "me-too" drug was "covered" by the approved NDA of the pioneer

drug in October 1962 (Section 107(c)(4)(C)), and, if not, whether the "me-too" drug in question was generally recognized as safe at that time (Section 107(c)(4)(B)).[13]

These are the kinds of questions the court below ruled FDA has no jurisdiction to determine. This ruling would transfer to the district courts an enormous volume of litigation, necessitating trials on complex medical and chemical issues, with the result that resolution of the "new drug" status of the numerous "me-too" drugs currently on the market would be substantially delayed.[14]

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[13] It is the position of FDA that a drug that is found to be a "me-too" would have been "covered" by an effective NDA at the time of the 1962 amendments and would therefore not be within the grandfather provision of Section 107(c)(4). The manufacturers contend that only NDA holders themselves are "covered" and that all "me-toos" are eligible for grandfather protection. Since neither the district court nor the court of appeals ruled on the merits of these contentions, the substantive issue whether plaintiffs' drugs are subject to the Act's effectiveness requirements is not directly involved in this petition. On remand, however, the issue would apparently be controlled by a decision of the same panel of the Fourth Circuit in *USV Pharmaceutical Corp.* v. *Richardson*, 461 F. 2d 223. In *USV*, the court held that "me-too" drugs produced by the same manufacturer who holds the pioneer NDA are "covered" and thus not "grandfathered," but made clear in its opinion that, contrary to FDA's contention, other manufacturers of "me-toos" would not be considered "covered." USV has been granted an extension of time within which to petition for a writ of certiorari.

[14] The NAS–NRC reports have led to the initial conclusion that approximately 1,350 drugs (involving more than 12,000 claimed uses), having NDAs approved between 1938 and 1962, fall within categories other than "effective" and are subject to possible withdrawal from the market. For each of these, it is estimated that there are, on the average, thirteen "me-too"

3. It is, we believe, both unwise and unnecessary for this obligation of initially determining the applicability of the Act to be imposed on district judges, whose dockets are already overcrowded and who generally do not have a background in medicine or chemistry.

Under the Act, the agency is assigned the primary role of determining whether, under statutory standards, new drugs ought to be made available to the public. The courts are assigned the important but secondary role of serving as the tribunal in which the agency can seek sanctions for non-compliance with the Act. The denial of agency power to determine the coverage of the Act it administers would reverse those roles, and the courts rather than the agency would become the primary tribunal for determining whether resort to the premarketing clearance procedures before the agency is necessary.

It is true that the agency cannot itself require a drug manufacturer to remove its product from the market. Contrary to the conclusion of the court below, however, we believe that the agency can provide an administrative remedy to determine whether "me-toos" are new drugs even though no procedure is

copies on the market for which no NDA was ever approved. In the present case, indeed, there are 23 plaintiffs, each of whom presumably manufactures a pentylenetetrazol product for which no NDA was ever issued, and each of whom presumably would have a right to bring a separate declaratory judgment proceeding. Neither the FDA nor the courts have the resources to deal effectively with this problem if it must be handled exclusively by the judiciary on a case-by-case basis.

specifically prescribed in the Act.[15] For the Administrative Procedure Act expressly enables FDA, like any other administrative agency, to issue "a declaratory order to terminate a controversy or remove uncertainty" (5 U.S.C. 554(e)). Such a declaratory order is subject to judicial review either in the district courts or the courts of appeals, depending upon the context in which it might be entered.

Thus, if the agency's declaratory order as to the status of a particular drug is unaccompanied by an order denying or withdrawing approval of an NDA, the order would be reviewable in the district courts,[16] since the Federal Food, Drug, and Cosmetic Act limits direct court of appeals review to orders denying or withdrawing approval of an NDA (Section 505(h), 21 U.S.C. 355(h)). If, however, the agency's determi-

[15] It is arguable that in circumstances involving technical questions in which agencies have special expertise, the courts should be required to defer to the agencies under the primary jurisdiction doctrine. See, *e.g.*, *United States* v. *Western Pacific R. Co.*, 352 U.S. 59, 62–70. In the present case, the government argued in the district court that FDA had primary jurisdiction and that the declaratory judgment action should be dismissed. Cf. *Far East Conference* v. *United States*, 342 U.S. 570, 576–577. But after the district court had ruled that it had concurrent jurisdiction, thereby rejecting the primary jurisdiction contention, it nevertheless referred the "new drug" question to the agency in the exercise of its equitable discretion. The government acquiesced in this determination and did not raise the primary jurisdiction argument on appeal. Consequently it is not presented in this petition. The agency believes, however, that where its regulations provide a uniform procedure for determination of issues within its responsibility, it has primary jurisdiction, and it will continue to assert this position where appropriate.

[16] Cf. *Citizens to Preserve Overton Park* v. *Volpe*, 401 U.S. 402.

nation of the "new drug" issue is made in a proceeding which results in the denial or withdrawal of an NDA, it would be reviewable, along with the denial or withdrawal order, in a court of appeals pursuant to Section 505(h).[17]

As the *Ciba Corporation* decision recognized, the power of the agency to determine administratively whether the Act's premarketing clearance procedure is applicable to particular drugs follows by necessary implication from the terms of the Act and the responsibilities it imposes.

For these reasons, we believe that the district court in the present case properly referred to the agency the question whether plaintiffs' drugs are subject to the Act's premarketing clearance procedure. The declaratory judgment remedy is discretionary. *Abbott Laboratories* v. *Gardner,* 387 U.S. 136, 148. The district court's decision to withhold that remedy until the agency, with the benefit of its expertise, had made a determination of the complex legal and factual issues involved was a permissible and appropriate exercise of its equitable discretion.

The court of appeals' reliance (App. A, *infra,* pp. 15a–16a) on the difference between the question involved in an agency proceeding for the approval or withdrawal of an NDA (safety and effectiveness in fact) and in a judicial enforcement proceeding (general recognition of safety and effectiveness) does not support the court's conclusion that the agency may never determine the latter issue in an administrative proceeding. The agency is at least as compe-

[17] *Ciba Corporation* v. *Richardson, supra.*

tent to decide that issue initially as are the district courts, if not more so. Indeed, the district court here frankly acknowledged that the agency is the "more able arbiter" of that question (App. C, *infra*, p. 27a).

Nor is the power of the courts to determine in an enforcement proceeding whether a particular drug is subject to the Act's premarketing clearance requirements a ground for concluding that the agency may never initially decide that question. Enforcement proceedings are the last resort under the statutory scheme; the threat of these enforcement proceedings, including criminal prosecution, is designed to channel manufacturers to the agency for premarketing clearance in the first instance.

There is, in short, no persuasive legal justification for the holding below that FDA has no authority to decide the threshold question whether the Act's premarketing clearance procedure applies to particular drugs. Unless overturned, that holding will impede substantially the agency's efforts to remove from the market drugs whose effectiveness cannot be shown. Achievement of one of the principal goals of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act—ensuring that drugs available to consumers are both safe and effective—thus would, at a minimum, be seriously delayed.[18]

[18] Only recently, FDA was criticized by a district judge for lack of expedition in carrying out this program. *American Public Health Ass'n.* v. *Veneman*, D.D.C., Civ. Action No. 1847-70, decided August 23, 1972 (holding that FDA must release to the public the NAS-NRC effectiveness reports it has not yet made public).

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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OCTOBER 1972.

# APPENDIX A

## United States Court of Appeals for the Fourth Circuit

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO., APPELLANTS

*v.*

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, APPELLEES

Appeal From the United States District Court for the District of South Carolina, at Greenville. Robert W. Hemphill, District Judge

Argued December 8, 1971—Decided May 23, 1972

Before WINTER, RUSSELL, and FIELD, Circuit Judges

*George F. Townes* (*Sol E. Abrams* on brief) for Appellants, and *Charles R. McConachie,* Attorney,



477-696—72——4

Department of Justice (*Will Wilson*, Assistant Attorney General, *John L. Murphy*, Chief, Administrative Regulations Section, *William W. Goodrich*, Assistant General Counsel, Food, Drugs, and Environmental Health Division, *Robert N. Anderson*, Attorney, United States Department of Health, Education, and Welfare, and *Howard S. Epstein*, Attorney, Department of Justice, on brief) for Appellees.

RUSSELL, *Circuit Judge:* This appeal turns on a construction of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1962.[1] 21 U.S.C. 301, *et seq.* This statute requires pre-marketing approval and clearance of any "new drug" by the Secretary of Health, Education, and Welfare.[2] The term "new drug" is defined as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condi-

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[1] There was an earlier Food and Drug Act of 1906. 34 Stat. 768 (1906). It did not provide for any pre-marketing review of the safety of drugs. The sulfanilamide episode in 1938 prompted the enactment of the Federal Food, Drug and Cosmetic Act of that year to replace the earlier Act and to provide, *inter alia*, for such pre-marketing review of "new drugs". See C. W. Dunn, *Federal Food, Drug and Cosmetic Act—A Statement of Its Legislative Record*, pp. 1316–27 (1938). The fears generated by the thalidomide tragedies gave the impetus for the Amendments of 1962. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, 185 at p. 191, n. 45 (1971).

[2] Section 355(a), 21 U.S.C.

The actual approval of a "new drug" under the Act is normally processed by the Food and Drug Administration (FDA) in the Department of Health, Education and Welfare (HEW), and the approvals, when granted, are generally referred to as New Drug Approvals (NDAs). FDA, when used herein, refers to the Food and Drug Administration, and NDA is intended to describe an approval by FDA of a "new drug" application under the Act.

tions prescribed, recommended, or suggested in the labeling thereof * * *."[3] From a denial of a pre-marketing approval or a withdrawal of a previously given approval, an appeal, originally to the District Court, now to the Circuit Court of Appeals, is authorized.[4] Drugs, which do not fit the definition of a "new drug"[5] do not require FDA clearance for marketing. There is no provision in the Act for administrative determination whether a particular drug is a "new drug" nor for any right of appeal from any such determination. The FDA sometimes offers to render "informal advice" as to whether it considers a product a "new drug" but it uniformly designates such opinion "advice".[6] Accordingly, the responsibility for determining whether its product is a "new drug", requiring pre-marketing clearance by FDA, rests on the manufacturer, who must act at its peril.[7] If it makes an incorrect determination and seeks to market without FDA clearance a drug meeting the definition of a "new drug", it lays itself open to drastic judicial procedures that may be invoked by FDA, i.e.: The product may be seized in an *in rem* action instituted by the Government;[8] its sale may be enjoined in an action

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[3] Section 321(p)(1), 21 U.S.C.

See, also, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445, n. 2:

"The statutory definition of the phrase 'new drug' controls this case, regardless of any other meaning attributable to the phrase or to the word 'new' by common understanding or other authority."

[4] Section 355(h), 21 U.S.C.

[5] 21 C.F.R. 130.39.

[6] Cf. *United States* v. *Dotterweich* (1943) 320 U.S. 277, 281, where, speaking of the Act of 1938, the Court said:

"In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

[7] Section 334, 21 U.S.C.

begun by the Government;[8] in addition, the manufacturer may be subjected to criminal action.[9] All these remedies must be prosecuted in the District Court and the role of the Secretary is that of plaintiff or prosecutor. The Act thus establishes two forums for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined "new drug", with right of appeal from a denial of approval, or withdrawal of a previous approval, to the District Court, later changed to the Court of Appeals; the other is judicial and is intended to make effective and give strength to the requirement that "new drugs" be cleared as safe before marketing by providing the Government with certain potent judicial remedies, *available exclusively in the District Court.*

Under the 1938 Act, a new drug was one "not generally recognized by experts * * * as safe for its intended use." The Amendments added "effectiveness" as well as "safety" to the definition. Simply stated, the change effected by the Amendments was that, whereas prior to the 1962 Amendments a drug which was generally recognized as safe was not a "new drug", the Amendments defined a drug as "new" if it were not generally recognized as both safe *and effective.* Furthermore, they replaced the provision for automatic approvals of applications not disapproved within a fixed time with a requirement of a positive act of approval on the part of FDA.[10] They proceeded to provide that the Secretary must find as a basis for clearance of a new drug not only safety but "substantial evidence" of effectiveness, "consisting of adequate and well-controlled investigations, including clinical inves-

[8] Section 332, 21 U.S.C.
[9] Section 333, 21 U.S.C.
[10] Section 355(c), 21 U.S.C.

tigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." The applicability of these amendments, including the revised definition of "new drug" to drugs already marketed, either under previously issued NDAs, or as "old drugs" requiring no FDA approval, was carefully spelt out in the Amendments and certain "grandfather rights" were granted. For all previously NDA'd drugs, the Amendments conferred a grace period of two years after the effective date of the Amendments within which to prepare evidence to satisfy the new requirement of efficacy added by the revised definition of "new drug"; during that "transitional" period no revocation or withdrawal of approval because of a lack of substantial evidence of efficacy of such drugs was permitted.[11] For a drug, however, which on the day prior to the enactment of the Amendments was (1) being "commercially used or sold in the United States," (2) "was not a new drug as defined by" the pre-Amendment statute and (3) "was not covered by an effective (new drug application, * * *" "on the day immediately preceding the enactment date" of the Amendments, there was a permanent exemption from the efficacy provisions of the Amendments so long as the drug's labeling remained the same.[12] In summary, these provisions required

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[11] Section 107(c)(3), P.L. 87-781, Section 321, Supplement 1972, 21 U.S.C.

[12] Section 107(c)(4), P.L. 871-781, Section 321, 1972 Supplement, 21 U.S.C.; see, also, *Tyler Pharmacal Distrib. Inc.* v. *U.S. Dept. of Health, E. & W.* (7th Cir. 1969) 408 F. 2d 95, 99.

It should be noted that Section 321(p)(1) provides a "grandfather clause" applicable to pre-1938 drugs. This clause is not relevant to this action, which is concerned with drugs introduced between 1938 and 1962, and the subsequent references to "grandfather clause" in this opinion are to section 107(c)(4).

that, "Those drugs which had obtained effective NDAs must be proven efficacious after two years; those which had not need never be proven efficacious so long as they had become safe prior to the 1962 Amendments." [13]

The "grandfather clause" set forth in Section 107(c)(4) simply continues for the products satisfying its criteria the pre-1962 definition of a "new drug". Its effect is to assure that a drug which was generally recognized by qualified experts as safe for the purposes recommended for its use on October 9, 1962, need not be NDA'd as *effective* under the new requirements for the issuance of an NDA as a "new drug". But any drug, whether requiring an NDA or not, whether a "new drug" or an "old drug", is subject to the misbranding provisions of the Act and may be proceeded against on that basis. A false claim of

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[13] Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, p. 196 (1971).

See, also, *United States* v. *Allan Drug Corp.* (10th Cir. 1966) 357 F. 2d 712, 719, note 9, quoting from the Supplemental Report of the Senate Committee on Drug Amendments of 1962, as set forth in the notes to Section 321, 21 U.S.C.:

"Thirdly, in the case of a drug on the market which was never subject to the new-drug procedure before, the amendments to the new drug definition relating to drug effectiveness would not apply to existing labeling claims."

In the Conference Report of the House Managers on the Amendments, it was stated that the Amendments included "the Senate language providing with respect to existing label claims of drugs that have never previously been subject to the new-drug procedure substantially the same savings provisions as the corresponding provision of the House bill (Section 197(d))." *U.S. Code Congressional and Administrative News*, 87th Congress, 2d Session (1962), p. 2932. Again, in H.R. Rep. #2526, p. 23, it is stated that the exemption granted by the "grandfather clause" applies "to existing claims of drugs that have never been subject to the new-drug procedure".

either safety or effectiveness constitutes misbranding, rendering a drug subject to both civil and criminal penalties. *United States* v. *Article of Drug Labeled Decholin* (D.C. Mich. 1967) 264 F. Supp. 473, 482–3; *United States* v. *Lanpar Company* (D.C. Tex. 1968) 293 F. Supp. 147, 153–4.[14] Accordingly, in *United States* v. *Guardian Chemical Corporation* (2d Cir. 1969) 410 F. 2d 157, a drug manufacturer was acquitted of a charge of marketing a "new drug" without securing an NDA, but was convicted under a separate count of the indictment charging misbranding. "Thus", as one commentator has aptly stated, "the amplications of the FDA's authority (as granted by the 1962 Amendments) is (was) not due to the absence of power to proceed against ineffective drugs, but rather to authorize the exercise of that power at the initial stage, that is, *before* marketing, and also to shift the burden of proof to the applicant." Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments,* 19 Food, Drug, Cosmetic Law Journal, 110, at p. 116 (1964).[15]

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[14] See, also, *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 548:

"A good case could certainly be made that, quite apart from this, the 'efficacy' of a drug is necessarily related to the use recommended."

[15] See, also, Senate Report #1744, *U.S. Code Congressional and Administrative News*, 87th Cong., 2d Sess. (1962), pp. 2892 and 2893, where, in justifying the Amendments, it is stated:

"* * * where a drug is essentially innocuous, it (FDA) must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. In such cases the Food and Drug Administration may proceed against the drug manufacturer by seizure of the drug for misbranding. However, the Department believes that the manufacturer should satisfy the

The plaintiffs, manufacturers of a prescription drug containing pentylenetetrazol and nicotinic acid, claim the protection of the "grandfather clause" included in Section 107(c)(4) for their products and that contention represents the substantive issue in this case. It is undisputed that plaintiffs had marketed their product commercially for many years prior to and on October 9, 1962,[16] without an NDA under the claim that it was not a "new drug" within the definition of the Act, and therefore required no NDA. Such claim was supported, it is asserted, both by previous informal advice of the Secretary and by the general recognition of the safety of such product by "experts qualified by scientific training and experience" to make such evaluation. The defendants, the Secretary of HEW and the Commissioner of Food and Drugs, in their brief, concede that "Over the years since 1938" and until 1968, the Food and Drug Administration had given the opinion that certain pentylenetetrazol combinations similar to those of the appellant were not "new drugs."[17] Moreover, the District Court ob-

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Food and Drug Administration that his product is effective for the purposes claimed before it is marketed. * * * No question of safety is involved, and the Food and Drug Administration presently has ample power, including seizure, to proceed against any safe drug for which unsupported claims of effectiveness are made."

[16] This was the day "immediately preceding the enactment date" of the Amendments of 1962.

[17] It is, of course, axiomatic that such opinions or advice can create no estoppel against the Government. *AMP Incorporated* v. *Gardner* (D.C.N.Y. 1967) 275 F. Supp. 410, 412, n. 1, aff. 389 F. 2d 825, cert. den. 393 U.S. 825, reh. den. 395 U.S. 917. The most that can be claimed for such opinions is that they lend color and good faith to the plaintiffs' claims. FDA not only has the right but is obligated to change its opinion if it learns its prior position was erroneous. *United States* v. *60 28-Capsule Bottles, More or Less, etc.* (D.C.N.J. 1962) 211 F. Supp. 207, 215, aff. 325 F. 2d 513.

served in its opinion that there was "no contention (by the FDA) that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs." On this basis, the plaintiffs contended that they met exactly the criteria established for exemption from the requirements of general recognition by qualified experts of the effectiveness of their products as provided in the permanent grandfather section of the 1962 Amendments.

Prior to the filing of this action, however, the defendants withdrew their advice that products such as those distributed by the plaintiffs were "old drugs" and contended that such products did not qualify for exemption under the "grandfather clause", Section 107(c)(4). The basis for this contention was the claim (1) that these drugs were not generally recognized by qualified experts as safe as of the effective date of the Amendments of 1962 and (2) that they were "me-too" drugs, whose marketability without FDA clearance depended in turn on the NDAs granted the basic drug, and for that reason must be regarded as drugs covered by an effective NDA on the effective date of the Amendments.[18] Faced with this threat, the plaintiffs

[18] The defendants assert that three "new drug" applications filed by other manufacturers and earlier approved by the FDA covered drugs similar in every particular to those marketed by the plaintiffs. Proceedings for withdrawal of the approval of such "new drugs" had been begun by FDA in advance of the filing of this action. In fact, such proceedings to a large extent prompted this action. It is the contention of the defendants that the withdrawal of what they describe as "the primary NDAs" operates to remove the marketability from what they assert are the "me-toos" or non-NDA'd drugs which are similar to other drugs which have secured effective NDAs. The plaintiffs deny that their drugs are like those previously NDA'd.

began this action for a declaratory judgment sustaining their right to exemption from proof of the effectiveness of their product and for injunctive relief awaiting the disposition of their claim for exemption. The defendants directed against the complaint a motion to dismiss or for summary judgment, which, in essence, (1) asserted primary jurisdiction in the Secretary to determine whether the products of the plaintiffs met the requirements for exemption under Section 107(c)(4), particularly whether they were "new drugs", requiring pre-marketing approval under the Act, (2) denied the propriety of a declaratory judgment action, and (3) claimed that the products of the plaintiffs were "new drugs" which did not qualify for exemption under the "grandfather clause".

The District Court sustained the right of the plaintiffs to maintain a suit for a declaratory judgment and the jurisdiction of the Court in such action to determine judicially whether the products of the plaintiffs

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They argue that those NDA'd products, unlike theirs, are intravenously administered or are a compound containing, in addition to the components of plaintiffs' drugs, reserpine. Such changes in formula or method of administering vitiated any claim by their manufacturers that they were marketing an old drug and required an approval as a new drug. The plaintiffs assert their drugs are not subject to any such disability. These, however, are questions of fact not relevant to the simple question of jurisdiction presented by this appeal and may be inquired into on remand. Even if the products of the plaintiffs be deemed "me-too" drugs (i.e., simply "a copy of a pioneer drug which preceded it on the market"), it is by no means clear that they do not "meet the requirements for section 107(c)(4) protection" and the argument of the Government to the contrary has been described as "lacking in merit." See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown Law Journal, 185 at p. 203–207 (1971); Hagan, *Grandfather Protection under the Drug Amendments of 1962*, 19 Food Drug Cosmetic Law Journal, 119, at p. 125 (1964).

were "new drugs", on the effective date of the Amendments, and whether they were or were not entitled to the benefits of the "grandfather clause".[19] However—and this is the nub of the controversy between the parties on this appeal—it concluded that the Secretary had concurrent jurisdiction to determine whether plaintiffs' products were "new drugs", requiring premarketing clearance, and that, because of the greater expertise of the Secretary in the field, it deferred to the Secretary's assumed jurisdiction to determine whether the drugs of the plaintiffs came within the exemption provided by the "grandfather clause". It enjoined any action against the plaintiffs and their products until the plaintiffs had been accorded a hearing before the Secretary on the issue of the qualifications of these drugs for protection under the "grandfather clause". It is the conclusion of concurrent jurisdiction in the Secretary and deference to that assumed concurrent jurisdiction from which the plaintiffs have prosecuted this appeal.

The defendants, on the other hand, have not cross-appealed and have accordingly acquiesced in the decision of the District Court that the action is properly

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[19] In support of the right of the plaintiffs to maintain a suit for declaratory judgment, the District Court relied on *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136 and the companion case of *Toilet Goods Assn.* v. *Gardner* (1967) 387 U.S. 158. Additional support for such right is found in *AMP, Incorporated* v. *Gardner, supra; Durovic* v. *Richardson* (D.C. Ill. 1971) 327 F. Supp. 386; *Lemmon Pharmacal Co.* v. *Richardson* (D.C. Pa. 1970) 319 F. Supp. 375. The right of the Court to determine the applicability of the "grandfather clause" is equally clear and has been sustained in *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445; and *United States* v. *Article Consisting of 36 Boxes, etc.* (D.C. Del. 1968) 284 F. Supp. 107, 112, n. 13, aff. 415 F. 2d 369.

maintainable as a declaratory judgment proceeding under Section 2201, 28 U.S.C. and that the District Court has jurisdiction over the substantive issue in this case, i.e., whether plaintiffs' products are "new drugs", as defined in the Act. The question in the case is thus whether the Secretary has concurrent jurisdiction to determine whether a drug is a "new drug" under the Act or whether that issue is cognizable only in the District Court. Contrary to the conclusion of the District Court, we conclude that the Act confers no such jurisdiction on the Secretary and, therefore, no basis for any deference by that Court to the concurrent jurisdiction of the Secretary.

The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or a new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a "new drug" requiring pre-marketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or initiator or either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a "new drug". There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a "new drug" application or to halt the marketing of a drug for which there is no approval by the Secretary. It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declaratory

judgment action.[20] Moreover, when FDA undertook its new responsibilities under 1962 Amendments, it sought merely to review "the efficacy of *all new drugs that had been cleared,* for safety only, between 1938 and October 10, 1962"[21] (Italics added) and enlisted the services of the National Academy of Sciences-National Research Council for this limited task. It did not assert the right to review, or assume the burden of reviewing, for efficacy, drugs such as those involved here, which had been commercially marketed on the basis of a general recognition of safety without an effective NDA as of the effective date of the 1962 Amendments. It, thus, recognized that its adjudicatory rights extended merely to the approval, or the withdrawal of approval,[22] of a drug embraced in a "new drug" application that had been approved. This confirms the conclusion that the halting of the marketing of a drug, for which there is no NDA, may not be by administrative action but must be by an injunction or *in rem* seizure proceeding, in which the Secretary appears, not in a judicial but in a prosecutorial role.[23] Those are the procedures prescribed and available to

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[20] See, *Hynson, Westcott & Dunning, Inc.* v. *Richardson* (Civ. No. 21112, D. Md., decided 9/16/70); and *Ciba Corp.* v. *Richardson* (Civ. No. 1210–70, D.N.J., decided 3/10/71); but cf., *Lemmon Pharmacal, supra.*

[21] See *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 539, and 31 F.R. 9426.

[22] The authority of the Secretary to withdraw an approval of any "new drug" application filed under the Act of 1938 after hearing is specifically granted by Section 355(e), 21 U.S.C.

[23] Of course, in a proper case the Government may also institute criminal proceedings in the District Court. See Section 333, 21 U.S.C.

the Government under the Act.[24] The Secretary, it is true, has offered to provide "advice" on whether a product meets the qualification of an old drug but he categorizes his action in such instances as merely "advice" and makes no claim of finality therefor. Nor is there, as we have already observed, any provision for judicial review of such "advice".[25] The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a "new drug" application.[26] That this is so follows from the limitations placed by the Act on judicial review of the decisions of the Secretary. The Secretary himself asserted, shortly after the enactment of the 1962 Amendments, in *Turkel* v. *Food and Drug Administration, Dept. of H.E.W., supra,* at p. 845, that the Act "grants a right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application". In keeping with the Secretary's contention as to the extent of his adjudicatory powers, the Court in that case held that the right of appeal from an order of the Secretary "applies only to an order of the Secretary refusing or

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[24] Cf. *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F. 2d 713, 718, cert. den. 385 U.S. 899, in which the Secretary is quoted to the effect that, " 'As to drugs already on the market that have never been subject to the new-drug procedure but are not generally recognized as effective, the burden remains on the Government to prove *in court*, insofar as unchanged labeling claims are concerned, they do not have their claimed effect. If the labeling claims are changed, however, these must be approved under the new-drug procedure.' " (Italics added.)

[25] See *Turkel* v. *Food and Drug Administration, Dept. of H.E.W.* (6th Cir. 1964) 334 F. 2d 844, 846, cert. denied 379 U.S. 990, rehearing denied 380 U.S. 927: "The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute."

[26] Section 355(b), 21 U.S.C.

withdrawing approval of an application for sale and distribution of a new drug" (at pp. 845–6). It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed. Yet this is the unusual situation that would be presented if the Secretary were held to have jurisdiction to adjudicate whether a drug meets the statutory criteria of a "new drug".[27]

The District Court, in finding concurrent jurisdiction, held that "This grant of authority to approve or withhold approval of new drug application, * * * necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which required an approved new drug application for lawful interstate shipment." This reasoning assumes that an application for approval by the Secretary under the Act poses as its initial issue whether the product is a new drug. No such issue is posed by the application. The very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a "new drug"; otherwise, there would be no reason to file the application. As a matter of fact, in the prescribed form of application, the applicant describes his product as a "new drug". 21 C.F.R. 130.4. The applicant makes the determination whether his product is a "new drug" and whether he must file for pre-marketing clearance by the Secretary. And when filed, the application puts in issue only one question: Is the article safe and effective? That and that alone is the issue to be considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different

[27] Cf., *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136, at p. 140.

from that presented when there is an issue whether a drug fits the statutory definition of "new drug" in the Act. The criterion for ascertaining whether a product is within statutory definition of "new drug" under the Act is not safety and effectiveness *per se,* which, as we have observed, is the issue before the Secretary in connection with application for approval of a "new drug", but "whether the government has shown by a preponderance of the evidence that the drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof." [28] That is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act. See, for instance, *United States* v. *Articles of Drug Labeled "Quick-O-Ver", supra; United States* v. *41 Cases, More or Less* (5th Cir. 1970) 420 F. 2d 1126, 1128; *United States* v. *Article of Drug, etc., supra,* at p. 392;

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[28] *United States* v. *Articles of Drug Labeled "Quick-O-Ver", supra,* at pp. 445–6.

See, also: *AMP, Incorporated* v. *Gardner, supra,* at p. 831:

"But the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education, and Welfare for a determination as to safety, adequacy of testing, etc."

*United States* v. *Article of Drug, etc.* (5th Cir. 1969) 415 F. 2d 390, 392:

"Both sides agree that the nature of expert opinion about Furestrol, and not its actual safety or effectiveness, is the ultimate fact issue."

Cf., *United States* v. *Seven Cartons, More or Less, etc.* (7th Cir. 1970) 424 F. 2d 1364, 1365.

*United States* v. *Article . . . Consist. of 216 Carton* (2d Cir. 1969) 409 F. 2d 734, 742; *United States Article Consisting of 36 Boxes, etc., supra,* at p. 113; see, also, *United States* v. *Article of Drug, etc.* (D.C. Md. 1971) 331 F. Supp. 912, 915–7. That was one of the issues resolved in the declaratory action of *Lemmon Pharmacal Co.* v. *Richardson, supra.*[29] It is manifestly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it. In the absence of any statutory review proceedings within which they may assert their claim of exemption, the plaintiffs are not to be compelled to proceed at their peril, subject to the possibility of both civil and criminal penalties, but are entitled to seek relief by way of a declaratory judgment action. The District Court should accordingly have retained jurisdiction and proceeded to determine whether the plaintiffs' drugs met the criteria for exemption under Section 107(c)(4). We deem it premature for us to consider at this stage whether plaintiffs' products meet such criteria. That issue was not developed in the record before, or ruled on by, the District Court.[30] Upon remand, the issue can be considered by the Court in the light of the record that may be made by the parties.

*Remanded, with directions.*

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[29] In discussing this case, the commentator in 60 Georgetown Law Journal, p. 199, note 87, says:

"In *Lemmon Pharmacal*, the Court, while noting that determining safety and efficacy would normally be within the primary jurisdiction of the agency, concluded that the question of section 107(c)(4) protection was properly before it."

[30] See *United States* v. *Article Consisting of 36 Boxes etc., supra,* at p. 113.

## APPENDIX B

[Filed, May 23, 1972, Samuel W. Phillips, clerk.]

United States Court of Appeals for the Fourth Circuit

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., ET AL., APPELLANTS

*v.*

ELLIOTT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, APPELLEES

*Judgment*

Appeal from the United States District Court for the District of South Carolina.

This cause came on to be heard on the record from the United States District Court for the District of South Carolina, and was argued by counsel.

On consideration whereof, It is now here ordered and adjudged by this Court that the judgment of the said District Court appealed from, in this cause, be, and the same is hereby, reversed. The case is remanded to the United States District Court for the District of South Carolina, at Greenville, with directions consistent with the opinion of this Court filed herewith.

SAMUEL W. PHILLIPS,
*Clerk.*

## APPENDIX C

[Original filed, February 10, 1971, Miller C. Foster, Jr., clerk]

In the District Court of the United States for the District of South Carolina, Greenville Division

Civil Action No. 70–1001

O'NEAL, JONES & FELDMAN, INC., BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO., PLAINTIFFS

*v.*

ELLIOT P. RICHARDSON, SECRETARYY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, DEFENDANTS

*Order*

This is a civil action for declaratory and injunctive relief brought by twenty-four pharmaceutical com-

panies aggrieved by the action of the Food and Drug Administration (hereinafter F.D.A.) respecting drugs containing pentylenetetrazol. The events leading to the commencement of this action may be summarized as follows: In August 1969 the F.D.A. announced in the FEDERAL REGISTER its intention to initiate proceedings to withdraw approval of new drug applications for two drugs containing pentylenetetrazol and nicotinic acid. (34 F.R. 13673) The drugs covered by those applications differed from those manufactured by the plaintiffs herein in that the product covered by one application was injected intravenously and the other application contained a third active ingredient, reserpine. The published notice invited the submission of data on the efficacy of the products by any interested person who might be adversely affected by the removal from the market of the drugs covered by the new drug applications. The notice further stated:

> Promulgation of the proposed order will cause any drug for human use containing the same active substances to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

None of the plaintiffs herein responded to the notice and in May 1970, a second notice was published stating that substantial evidence of the effectiveness of the drugs covered by the new drug applications had not been provided and that the approval of the applications would be withdrawn. Notice was also given that any affected person desirous of a hearing on the question should so elect within 30 days (35 F.R. 7749). That notice contained language concerning the effect on drugs other than those covered by the applications to be withdrawn substantially identical to the language of the August notice set out above.

In September 1970 the F.D.A. published its order withdrawing approval of the two new drug applications mentioned above and directing the recall of outstanding stocks of the drugs. 35 F.R. 14412.

Pursuant to its revocation of the two new drug applications, the F.D.A. took steps to effect the removal from the market of drugs containing pentylenetetrazol manufactured by various of the plaintiffs. By their complaint in this action the plaintiffs seek declaratory judgment determining the validity and enforceability of the order of the Secretary as it concerns their drugs and injunctive relief pendente lite. The defendant moves that the action be dismissed for want of jurisdiction and failure to state a claim for which relief can be granted.

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, *et seq.*) effective in 1938, gave preclearance authority to the Food and Drug Administration to regulate the distribution of new drugs by a system of new-drug applications which had to be obtained before distribution of the drug in interstate channels was allowed. The early definition of new drugs, however, gave the Agency power to regulate these drugs and approve them on the basis of safety alone. The drug companies were not required to support their claims of effectiveness for the drug with appropriate medical data. Effective on October 10, 1962, the Act was amended to close this important gap in the regulatory power of the Agency. Under the provisions of the Act as amended, a drug not only must be proved safe, but also must be shown by "substantial evidence," to be effective for the indication and uses described in its labeling. The amendments also define "substantial evidence" as consisting of ". . . adequate and well-controlled investigations, including clinical investigations, by experts . . ." sufficient to

demonstrate that the drug works as claimed. [21 U.S.C. 355(d)]. The burden of producing evidence of effectiveness to support continued marketing of drugs which have already been cleared on the grounds of safety, is placed squarely on the drug manufacturers and distributors. [21 U.S.C. § 355(b)]. The Act as amended also gives the Secretary power to revoke approved new drug applications for several reasons among which is failure to submit substantial evidence of the effectiveness of the drug [21 U.S.C. 355(e)3]. It was pursuant to this authority that the Secretary issued the order by which the plaintiffs herein are aggrieved.

The Act grants the Secretary primary jurisdiction to make determinations regarding new drug applications and provides direct appeal from his orders to the circuit courts.[1]

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[1] 21 U.S.C. § 355(h). An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 23, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if sup-

The plaintiffs do not contend that this court has jurisdiction to consider the propriety of the Secretary's revocation of the two new drug applications. Rather they argue either that their drugs are not new drugs within the meaning of the Act or are within the grandfather clause;[2] and are therefore not subject to the Secretary's regulation of new drugs. The plaintiffs contend that seizure, injunction, or criminal prosecu-

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ported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the Court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

[2] 21 U.S.C. § 321(p). The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at

tion by the F.D.A. pursuant to 21 U.S.C. §§ 332–34 is imminent.[3] They urge that, rather than proceeding at their peril, they are entitled to declaratory relief adjudicating the merits of their respective contentions

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such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigation, been used to a material extent or for a material time under such conditions.

[3] The plaintiff Bentex Pharmaceutical Company received the following letter from the F.D.A.:

Nov. 4, 1970.

"This letter is written in reference to your products Benizol Tablets & Elizir, Benizol A-D Tablets, & Benizol Plus capsules & Elixir containing Pentylenetetrazol for human use.

"On September 12, 1970, an announcement published in the *Federal Register* setting forth the conclusion of the Food and Drug Administration that there is a lack of substantial evidence that drugs similar to yours are effective for the uses prescribed, recommended, or suggested in their labeling.

"Accordingly, the Commissioner of the Food and Drug Administration has withdrawn approval of the applicable new drug applications for such drugs.

"The withdrawal of all previously approved new drug applications causes any similar drug to be a new drug for which an approved new drug application is not in effect. Because these are no longer regarded as legal products, any such drug on the market is subject to regulatory proceedings under the applicable provisions of the Federal Food, Drug, and Cosmetic Act.

"We request your reply within 15 days after receipt of this letter stating your intentions with respect to removal of all outstanding stocks of your product to the retail level."

concerning the status of their drugs.[4] They argue persuasibly that they are entitled to a day in court on that question prior to the seizure of their products and possible criminal prosecution.

The plaintiffs urge that they can only have that day in this court. The court does not agree. The Act gives the F.D.A. authority to proceed by seizure action, criminal prosecution, or injunction, [21 U.S.C. 332–334] to clear the channels of interstate commerce of drugs which have improperly avoided the new drug procedures. This grant of authority to approve or withhold approval of new drug application, or to proceed with regulatory action in the courts, necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment. The determination that a drug is a new drug is essential to any F.D.A. action regulating it by means of new drug applications. Therefore, the F.D.A. must have jurisdiction to make that determination.[5]

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[4] It appears that for a time drugs of the type in question were regarded as old drugs by the F.D.A. The record contains a letter dated Dec. 15, 1958 which reads in pertinent part as follows:

"As to your inquiry concerning the new drug status of a timed disintegration tablet containing Pentylenetetrazol 300 mg., Nicotinic Acid 150 mg.

"In our opinion this article is not a new drug as defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act when distributed as a prescription preparation under the labeling which you have submitted." Statements such as the above were, however, revoked by the Secretary [21 C.F.R. 130.39].

[5] Hymson, Westcott and Dunning, Inc. v. Finch, C.A. 2112, D. Md., decided September 16, 1970, on facts represented to the court to be similar to the present case held that the F.D.A. could consider and decide questions determining the status of a drug and that review of that determination would be available pursuant to 21 U.S.C. 355(h) set out at n. 1, supra.

The defendant, on the other hand, urges that this court does not have jurisdiction to consider and determine the status of the drugs in question, that the F.D.A. has primary and exclusive jurisdiction with appeal to the circuit court. That contention is likewise without merit. There is no doubt that the F.D.A. does have primary jurisdiction to make determinations concerning the safety and effectiveness of new drugs. Its expertise is necessary for consideration of the complex and technical nature of the factual issues to be evaluated.[6] That question is not, however, in dispute in this instance. The contention urged by the plaintiffs that its drugs are old or grandfathered, must turn upon the court's conclusion as to whether among qualified experts there was general recognition of the safety and efficacy of the drug. [*United States* v. *"Quick-O Ver"*, 274 F. Supp. 443 (1967)]. Counsel for the defendants acknowledged that the fact that the drugs were old or grandfathered would be a defense to be raised and considered in the district court when and if the F.D.A. sought sanctions against the plaintiff manufacturers.

The remaining question regarding the jurisdiction of this court is whether the action for declaratory judgment may be maintained in its present posture. The opinions of the Supreme Court in *Abbott Laboratories* v. *Gardner*, 387 U.S. 136 (1967) and *Toilet Goods Asso.* v. *Gardner*, 387 U.S. 158 (1967) convince this court that the present matter is properly before it. As pointed out in those cases, there is nothing in the Food, Drug, and Cosmetic Act [21 U.S.C. § 301, *et seq.*] which bars a pre-enforcement suit under the Ad-

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[6] See e.g Far East Conference v. United States, 342 U.S. 570 (1952); Tyler Pharmacal Dist. v. H.E.W., 408 F. 2d 95 (7th Cir. 1969); Lemmon Pharmacal Co. v. Richardson, C.A. 68-921, E.D. Pa. 1970.

ministrative Procedure Act [5 U.S.C. §§ 701–704] and the Declaratory Judgment Act [28 U.S.C. § 2201]. The language in the Secretary's announcement of May 20, 1970, of which the plaintiffs complaint and pursuant to which the Secretary apparently intends to proceed against them, is apparently final within the meaning of 5 U.S.C. § 704. (*Abbott,* supra, at 692) The letter of the F.D.A. set out above in note 4, indicates that action against the plaintiffs is imminent. The affidavits of the plaintiffs show that the threatened action will result in substantial injury to them. Therefore, this matter is properly before this court and the defendant's motion to dismiss is denied.

The court indicated above that the F.D.A. has jurisdiction to determine whether the drugs in question are new drugs. The court is of the opinion that, even though that determination can be made in this forum, the nature of the proof relevant to that issue makes the F.D.A. the more able arbiter of the question. However, if such determination is to be binding upon the plaintiffs in this action and the industry in general, parties interested in the status of drug combinations must be given an opportunity to be heard. They must be provided a day in court on the issue, during which a record can be made, on which record appeal to the circuit court can be had. That procedure would produce a resolution to the question which would bind the industry and remove the issue from subsequent, and perhaps numerous, enforcement actions. These plaintiffs quite properly point out that they have as yet had no opportunity to be heard on the question of whether their products are new drugs within the meaning of the Act; and it does not appear that such hearing could have been required of the F.D.A. by the plaintiffs. Evaluation of conflicting reports as to the reputation of drugs among experts

in the field is not a matter well left to a court without chemical or medical background. The court's opinion in this regard has influenced it considerably in its consideration of appropriate temporary relief.

The area of regulation of drugs is one which the court enters with great reluctance. However, the affidavits of the plaintiffs convince the court that they may suffer substantial business losses, perhaps unnecessarily, if the court refuses to grant temporary relief. As the court understands the record before it and the argument of counsel, there is no contention that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs. The court's order, being based upon this hypothesis, will be vacated upon a sufficient contrary showing by the defendant and, upon request by the defendant, the court will arrange to hear its proof in that regard.

The situation revealed by the record to date convinces the court that the status quo must be preserved until such time as the plaintiffs have an opportunity to be heard on the merits of their contention. Therefore, the court will enjoin the defendants from instituting actions against the plaintiffs on account of such of their products as are presently marketed, as contain combinations of pentylenetetrazol and nicotinic acid, are distributed by prescription, and are for treatment

of symptoms of senility in geriatric patients; and the defendants are hereby enjoined from instituting any action against the plaintiffs herein for the cause stated above until such time as there has been a determination that the products in question are new drugs. Recognizing the desirability of the F.D.A.'s making such determination, after a hearing of the matter, this court will defer further proceedings herein upon a showing by the defendants that such hearing will be held. It will dissolve the injunction herein ordered, and dismiss the presentation upon resolution of the question by the F.D.A. after a hearing.[7] Should the F.D.A. decline to hold such hearing, the matter must proceed to determination in this court.

And *It is so ordered.*

Robert W. Hemphill
Robert W. HEMPHILL,
*United States District Judge.*

COLUMBIA, SOUTH CAROLINA.
FEBRUARY 10, 1971.

[A true copy.
Teste: Miller C. Foster, Jr. Clerk, by: Deputy Clerk.]

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[7] A court has considerable discretion in proceeding in actions for declaratory judgment, and may dismiss such actions if they are pending in litigation elsewhere. Abbott Laboratories v. Gardner, 387 U.S. 136, 155 (1952).

## APPENDIX D

The Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040, as amended by the Harris-Kefauver Act, 76 Stat. 780, 21 U.S.C. 301 *et seq.* provides in part:

Section 201(p)(1) (21 U.S.C. 321(p)(1)):

> The term "new drug" means—(1) Any drug * * * the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use;

Section 505(a) (21 U.S.C. 355(a)):

> No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug.

Section 505(d) (21 U.S.C. 355(d)):

> If the Secretary finds, after due notice to the applicant * * * and giving him an opportunity for a hearing * * * that * * * (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is repre-

sented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof * * * he shall issue an order refusing to approve the application. * * * As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Section 505(e) (21 U.S.C. 355(e)):

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof * * *.

Section 505(h) (21 U.S.C. 355(h)):

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of

Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. * * *.

Section 107(c) of Public Law 87-781, 76 Stat. 788-789, note following 21 U.S.C. 321 (1970 ed.), provides in pertinent part:

* * * * *

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date [October 10, 1962] by virtue of paragraph (2) of this subsection—

* * * * *

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application * * * until * * *: (i) the expiration of the two-year period beginning with the enactment date * * *.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (c) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when inteneded solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

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